UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,488	01/15/2004	David G. Gorenstein	UTMB:1019RCE	5963

34725 7590 10/15/2008

CHALKER FLORES, LLP
2711 LBJ FRWY
Suite 1036
DALLAS, TX 75234

EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
10/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,488	GORENSTEIN ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-12,14-17 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-12,14-17 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/6/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Priority

The priority date for siRNA thioaptamers as recited in claims 7 and 10-12 is January 15, 2004, the filing date of the instant application, for the reasons set forth in the previous office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, 8, 9, 15-17 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baracchini et al. (US 5,801,154, of record) in view of Metelev et al. (US 5,652,355).

The claimed invention is directed to isolated thioaptamers 15-25 nucleotides in length that mediate gene silencing and comprise one or more ribonucleotide monophosphates, which are the equivalent of a phosphorothioate linkage, and further comprise deoxynucleotide phosphorothioates at non-adjacent positions. Thioaptamer is

defined in the specification on page 6 as encompassing antisense oligonucleotides and ribozymes. The thioaptamer may comprise a 3' OH group and may be composed of ribonucleotides or deoxyribonucleotides. The thioaptamer may be fully or imperfectly complementary to the target gene and the silencing can occur through repression of translation, mRNA cleavage or binding to a 3'UTR. The thioaptamers can comprise compositions with a carrier.

Baracchini et al. teach antisense oligonucleotides that are targeted to and inhibit multi-drug resistance associated protein. These antisense oligonucleotides are 8-30 nucleotides in length, are comprised of RNA or DNA, are targeted to numerous regions of the target gene, including the 3'UTR and are provided as compositions comprising a carrier (see claims 1 and 4-6 and columns 6-7). At column 3, lines 32-34 Baracchini et al. disclose that antisense oligonucleotides do not have to be 100% complementary to the target gene. It is known in the art that antisense inhibition occurs through an RNase H mechanism that cleaves mRNA and prevents translation of the mRNA into protein. Baracchini et al. teach at column 6 that antisense oligonucleotides can contain phosphorothioate linkages but do not explicitly teach incorporation of phosphorothioates at at least two ribonucleotide positions and at non-adjacent deoxynucleotide positions.

It was well known to those of ordinary skill in the art at the time the invention was made that nucleic acids can be easily substituted with phosphorothioate or phosphorodithioate linkages and that such substitutions provide nuclease resistance. Metelev et al. exemplify this concept at columns 4-5, teaching oligonucleotides that may comprise either phosphorothioate or phosphorodithioate linkages. Metelev et al. further

teach that optimization of variables in an oligonucleotide such as size and number and type of modified nucleotides is routine, teaching that,

> "The ability to vary the numbers and positions of phosphorothioate and/or phosphorodithioate internucleotide linkages, deoxyribonucleotides, and ribonucleotides or 2'-substituted ribonucleotides allows the investigator to examine in detail how each of these variables affects the parameters of nuclease resistance, duplex stability and RNase H activation. The ability to vary the size of the oligonucleotide allows examination of yet another parameter."

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the antisense oligonucleotides taught by Baracchini et al. with both RNA and DNA nucleotides and to substitute phosphorothioate linkages at two ribonucleotides and at non-adjacent deoxynucleotide positions. One would be motivated to produce the antisense oligonucleotides of Baracchini with both RNA and DNA nucleotides because Baracchini et al. teach that antisense oligonucleotides can comprise these nucleotides. Based on the teachings of Metelev et al. that varying the number and positions of substituted nucleotides such as phosphorothioates allows detailed examination of the effect of such variations, one of ordinary skill in the art would recognize the inclusion of two modified ribonucleotides and non-adjacent deoxynucleotides to be a matter of design choice and routine optimization made in order to produce an oligonucleotide having the best combination of properties for a desired application.

Thus, the invention of claims 1-4, 6, 8, 9, 15-17 and 37 would have been obvious, as a whole, at the time the invention was made.

Claims 1-4, 6, 7, 9 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. (WO 94/01550) in view of Metelev et al. (US 5,652,355).

The claimed invention is directed to isolated thioaptamers 15-25 nucleotides in length that mediate gene silencing and comprise one or more ribonucleotide monophosphates, which are the equivalent of a phosphorothioate linkage, and further comprise deoxynucleotide phosphorothioates at non-adjacent positions. In specific embodiments the thioaptamer comprises a 3' OH group and may be composed of ribonucleotides or deoxyribonucleotides. The thioaptamer can silence a gene can occur through mRNA cleavage.

Agrawal et al. teach self-stabilized oligonucleotides comprising a target hybridizing region and a self-complementary region. On pages 15-16 Agrawal et al. disclose the oligonucleotide is a single nucleic acid strand that forms a double stranded structure and the self-complementary region of the oligonucleotide is fully complementary to the hybridizing region to form a duplex. On page 8 Agrawal et al. disclose that the self-stabilized oligonucleotides are composed of ribonucleotides, deoxynucleotides and/or modified nucleotides. On pages 17, line 27 through page 18 Agrawal et al. disclose that the self-stabilized oligonucleotides can be administered to the cells of an animal to inhibit gene expression in the animals, which requires formulation with a pharmaceutically acceptable carrier. At page 14 Agrawal et al. disclose that the oligonucleotide can comprises phosphorothioate linkages but do not explicitly teach incorporation of phosphorothioates at at least two ribonucleotide positions and at non-adjacent deoxynucleotide positions.

It was well known to those of ordinary skill in the art at the time the invention was made that nucleic acids can be easily substituted with phosphorothioate or phosphorodithioate linkages and that such substitutions provide nuclease resistance. Metelev et al. exemplify this concept at columns 4-5, teaching oligonucleotides that may comprise either phosphorothioate or phosphorodithioate linkages. Metelev et al. further teach that optimization of variables in an oligonucleotide such as size and number and type of modified nucleotides is routine, teaching that,

> "The ability to vary the numbers and positions of phosphorothioate and/or phosphorodithioate internucleotide linkages, deoxyribonucleotides, and ribonucleotides or 2'-substituted ribonucleotides allows the investigator to examine in detail how each of these variables affects the parameters of nuclease resistance, duplex stability and RNase H activation. The ability to vary the size of the oligonucleotide allows examination of yet another parameter."

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the self-stabilized antisense oligonucleotides taught by Agrawal et al. with both RNA and DNA nucleotides and to substitute phosphorothioate linkages at two ribonucleotides and at non-adjacent deoxynucleotide positions. One would be motivated to produce the oligonucleotides of Agrawal et al. with both RNA and DNA nucleotides because Agrawal et al. teach that their oligonucleotides can comprise these nucleotides. Based on the teachings of Metelev et al. that varying the number and positions of substituted nucleotides such as phosphorothioates allows detailed examination of the effect of such variations, one of ordinary skill in the art would recognize the inclusion of two modified ribonucleotides and non-adjacent deoxynucleotides to be a matter of design choice and routine optimization made in order to produce an oligonucleotide having the best combination of properties for a desired application.

Thus, the invention of claims 1-4, 6, 7, 9, 14-16 and 37 would have been obvious, as a whole, at the time the invention was made.

Claims 1, 7, 10-12 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fosnaugh et al. (US 2003/0143732) in view of Metelev et al. (US 5,652,355).

The claimed invention is directed to isolated thioaptamers 15-25 nucleotides in length that mediate gene silencing and comprise one or more ribonucleotide monophosphates, which are the equivalent of a phosphorothioate linkage, and further comprise deoxynucleotide phosphorothioates at non-adjacent positions. In specific embodiments the thioaptamer comprises a double stranded RNA fully complementary to a target that silences the gene by mRNA cleavage, is part of a RISC complex, is produced by a DICER complex or is a siRNA.

Fosnaugh et al. teach that siRNAs are useful for a variety of therapeutic, diagnostic, agricultural, target validation, genomic discovery, genetic engineering and pharmacogenomic applications. Chemically-modified siRNAs are expected to improve various properties of siRNAs including increased *in vivo* nuclease resistance and/or improved cellular uptake. Specific embodiments of siRNAs and chemically modified siRNAs are taught at pages 3-8. Fosnaugh et al. teach chemically modified siRNAs including phosphorothioate modified backbones and the inclusion of deoxynucleotides in overhangs and as terminal cap moieties. Fosnaugh et al. specifically teach the use of phosphorothioate modifications in siRNAs but do not explicitly teach incorporation of

phosphorothioates at at least two ribonucleotide positions and at non-adjacent deoxynucleotide positions.

It was well known to those of ordinary skill in the art at the time the invention was made that nucleic acids can be easily substituted with phosphorothioate or phosphorodithioate linkages and that such substitutions provide nuclease resistance. Metelev et al. exemplify this concept at columns 4-5, teaching oligonucleotides that may comprise either phosphorothioate or phosphorodithioate linkages. Metelev et al. further teach that optimization of variables in an oligonucleotide such as size and number and type of modified nucleotides is routine, teaching that,

> "The ability to vary the numbers and positions of phosphorothioate and/or phosphorodithioate internucleotide linkages, deoxyribonucleotides, and ribonucleotides or 2'-substituted ribonucleotides allows the investigator to examine in detail how each of these variables affects the parameters of nuclease resistance, duplex stability and RNase H activation. The ability to vary the size of the oligonucleotide allows examination of yet another parameter."

While Metelev et al. discuss such optimization in terms of antisense oligonucleotides, those of ordinary skill in the art would recognize that such optimization could be performed on any nucleic acid.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the siRNAs taught by Fosnaugh et al. with both RNA and DNA nucleotides and to substitute phosphorothioate linkages at two ribonucleotides and at non-adjacent deoxynucleotide positions. One would be motivated to produce the siRNAs of Fosnaugh et al. with both RNA and DNA nucleotides because Fosnaugh et al. teach that siRNAs can comprise these nucleotides. Based on the teachings of Metelev et al. that varying the number and positions of substituted nucleotides such as phosphorothioates allows detailed examination of the effect of such variations, one of

ordinary skill in the art would recognize the inclusion of two modified ribonucleotides and non-adjacent deoxynucleotides to be a matter of design choice and routine optimization made in order to produce an oligonucleotide having the best combination of properties for a desired application.

Thus, the invention of claims 1, 7, 10-12 and 37 would have been obvious, as a whole, at the time the invention was made.

Response to Arguments

Applicants traverse each of the previously applied rejections by arguing the cited references do not teach all limitations of the claims. The rejections have been revised in view of the amendments to the claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight

(EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Primary Examiner
Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635